REMARKS

Entry of the foregoing amendments and favorable consideration of the subject application is respectfully requested in view of the following comments.

Claims 1, 11, 12, 14 and 34 are currently pending in this application. Claims 1, 14, and 34 have been amended and Claims 2-10, 13, 15-33 and 35 have been previously cancelled. Accordingly, claims 1, 11, 12, 14 and 34 are herewith represented for examination.

Claims 1, 14 and 34 have been amended to more particularly recite the invention as a combination of the specific compound of formula IA and a specified list of antitumor agents consisting of 5-fluorouracil, doxorubin, etoposide, irinotecan, topotecan and campthotecin, which combination exhibits a synergistic effect in the treatment of cancer. Antitumor agents cisplatin and carboplatin have been deleted.

Specifically, claim 1 has been restricted to the compound of formula IA, which is the form of general formula I originally recited in claim 10, in combination with at least one antitumor agent selected from the listed group of six such agents, 5-fluorouracil, doxorubin, etoposide, irinotecan, topotecan and campthotecin, culled from the original recitation of claim 1, with the added proviso, originally recited in now cancelled claim 2, that, if the antitumor agent 5-fluorouracil is present, the preparation may further contain leucovorin or be combined with a

separate leucovorin preparation.

Similarly, amended claim 14 has also been restricted to the compound of formula IA, which is the form of general formula I originally recited in claim 23, in combination with at least one antitumor agent selected from the listed group of six such agents, 5-fluorouracil, doxorubin, etoposide, irinotecan, topotecan and campthotecin, culled from the original recitation of claim 14, with the added proviso, originally recited in now cancelled claim 15, that, if the compound of formula IA is combined with the antitumor agent 5-fluorouracil, leucovorin may be further combined.

Furthermore, amended claim 34 has also been restricted to the compound of formula IA, which is the form of general formula I originally recited in claim 23, in combination with at least one antitumor agent selected from the listed group of six such agents, 5-fluorouracil, doxorubin, etoposide, irinotecan, topotecan and campthotecin, culled from the original recitation of claim 34, with the added proviso, originally recited in now cancelled claim 35, that, if the composition contains 5-fluorouracil, it may further contain leucovorin or may be combined with a separate leucovorin preparation.

Applicants respectfully submit that the foregoing amendments narrow the scope of the remaining pending claims in the present application placing them in condition for allowance or better condition for appeal and do not present any features requiring

further search. Furthermore, Applicants respectfully submit that no new matter has been added by the amendments herein, that these amendments are appropriate for entry at this time, and that the application is now in condition for allowance.

Double Patenting

The rejection of Claims 1, 11-12, 14 and 34 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of Kojiri, et al., (U.S. Patent No. 5,922,860) in view of Fukuda, et al. ("Synergism between Cisplatin and Topoisomerase I inhibitors, NB-506 and SN-38 in Human Small Cell Lung Cancer Cells", Cancer Research, 56, 789-93, 2/15/1996) has been maintained by the examiner for the reasons of record. The office action states:

> "The claims of the instant application are drawn to combinations of an indolocarbazole of formula Ia and an additional anticancer agent, such as cisplatin.
>
> Kojiri et al. teach that compounds having the same formula as those of formula Ia of the instant application and their use as antitumor agents. What is not taught is the combinations with additional anticancer agents.
>
> Fukuda et al. disclose synergistic combinations of NB-506 and cisplatin (see abstract-discussion on page 791). NB-506 is a structurally similar compound to that of formula Ia instantly claimed. Fukuda et al. state that the combination of cisplatin and a topoisomerase I inhibitor is a very interesting strategy for cancer chemotherapy (discussion).
>
> It would have been obvious to one of ordinary skill in the art at the time of the invention to use the topoisomerase I inhibitors of Kojiri et al. in

combination with cisplatin with these references before them. Fukuda et al. discuss the potential for synergism in cancer therapy when using cisplatin and a topoisomerase I inhibitor. Morover, it is noted that the compounds of formula Ia are very structurally similar to NB-506 us in Fukuda et al. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. ***In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).*** (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious). See also ***In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960)*** (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and ***Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992)*** (mixture of two known herbicides held prima facie obvious). Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the art disclosed indolocarbazole of Kojiri et al. with another antitumor agent, especially in light of the synergistic effects shown by Fukuda et al. One would have been motivated to combine these agents to form a new composition which would be used for the very same purpose, as an antitumor agent. Moreover, it is noted that the KSR decision forecloses the decision that teaching/suggestion/motivation is required in making an obviousness rejection.

Applicants argue that Kojiri et al. do not teach any combinations. Applicants also argue that Fukuda teaches combinations of NB-506 and additional anticancer agents, but NB-506 is divergent in structure as compared to the instant compound of formula Ia. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner believes that due to the close structural relationship between NB-506 as set forth in

Fukuda and formula Ia as in Kojiri, a skilled artisan would find it obvious to make a combination of anticancer drugs with the compound of Kojiri and additional agents of Fukuda with these references before them. Regarding the applicant's arguments drawn to Fukuda only guessing about the synergistic effects, this would at the minimum afford a skilled artisan an obvious reason to try to combine the agents as instantly claimed.

Applicants also argue that the structures of formula Ia and NB-506 are very different. The examiner respectfully disagrees. Regarding applicants noting that the instant compounds have -OH in the 2 and 10 positions and NB-506 has the -OH in the 1 and 11 positions, it is noted that claim 1 of Kojiri states that the -OH groups can be either in the 1 and 11 positions or the 2 and 10 positions, thus providing obviousness and motivation to have -OH at either sets of locations. The other difference is groups attached to the exocyclic amino moiety, NH-CHO versus NH-$CH(CH_2OH)_2$. However, Kojiri et al. also bridges the gap as the results of Table 1 show compounds with NH-CHO group have slightly lower activity versus compounds with NH-$CH(CH_2OH)_2$ groups attached. Thus rendering obvious and providing motivation to change the NH-CHO to a NH-$CH(CH_2OH)_2$ group.

Regarding applicant's arguments drawn to a "synergistic combination", it is noted these limitations are not in the claims and as such are not deemed to render unobvious the instant rejection."

As to claims 1, 11-12, 14 and 34 as amended herein, Applicants respectfully traverse the rejection because the prima *facie case* of obviousness has not been established.

As previously noted, an obviousness-type double patenting rejection is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" citing *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). "Therefore, the analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness

determination. In re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985)." (MPEP 804).

Thus, discussion of the law of obviousness under 35 U.S.C. 103 is appropriate.

The Patent and Trademark Office has the initial burden of producing a factual basis for a rejection under 35 U.S.C. § 103. In other words, the Patent and Trademark Office must establish a prima-facie case for obviousness. If examination does not produce a prima-facie case of unpatentability under § 103, then without more, the applicant is entitled to a grant of the patent. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ 2d 1443, 1444 (Fed. Cir. 1992). The issue of the prima-facie case for obviousness was visited by the Federal Circuit in *In re Thrift*, 63 USPQ 2002. In that case, the Federal Circuit stated the following:

> "To establish a prima-facie case of obviousness the Board must, *inter alia*, show 'some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.' *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ 2d 1596, 1598 (Fed. Cir. 1988). 'The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases, the nature of the problem to be solved.' *In re Kotzab*, 217 F.3d 1365, 1370, 15 USPQ 2d 1313, 1317 (Fed. Cir. 2000)."

63 USPQ 2d at 2006.

If the Primary Examiner has established a case for prima-facie obviousness, the burden then shifts to the applicant to

demonstrate why the claims are unobvious. See *Patents and the Federal Circuit, 5th Edition*, by Robert L. Harmon, § 4.7(b), page 185.

In *Graham v. John Deere Co.*, 383 US 1, 148 USPQ 459 (1966), the U.S. Supreme Court announced the test that has since become the standard guideline for assessing patentability under 35 U.S.C. § 103. Under that section of the Patent Statutes, the Supreme Court stated that the inquiry was as follows:

> "The scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined."

383 US at 17.

The inquiry as to when the issue of obviousness is to be resolved is that the inquiry is conducted "at the time the invention was made." 35 U.S.C. § 103. In attempting to reject claims under 35 U.S.C. § 103, there must be a reason or suggestion in the art for making the combination of features suggested by the Examiner other than knowledge learned from applicant's own disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ 2d 1529, 1532 (Fed. Cir. 1988). The test to be applied is whether the references taken as a whole would suggest the invention to one of ordinary skill in the art. *Medtronic Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1582, 220 USPQ 97, 110 (Fed. Cir. 1983). Inherent in the forbiddance of the use of hindsight is the forbiddance of picking and choosing various

features of different prior art references as a mosaic to recreate a facsimile of the claimed invention without a suggestion to combine them together in the references taken as a whole. *Akzo N.V. v. United States ITC*, 808 F.2d 1471, 1481, 1 USPQ 2d 1241, 1246 (Fed. Cir. 1986). Where the Examiner has picked and chosen various features from separate prior art references and has combined them together using applicant's own disclosure as the blueprint to do so, such a rejection is fatally flawed and must be reversed. *Heidelberger Druckmaschinenag v. Hantscho Commercial Products, Inc.*, 21 F.3d 1068, 1072, 30 USPQ 2d 1377, 1379-80 (Fed. Cir. 1994); *In re Geiger*, 815 F.2d 686, 688, 2 USPQ 2d 1276, 1278 (Fed. Cir. 1987). It is improper to use the inventor's patent application as an instruction book on how to reconstruct the prior art. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1574, 1 USPQ 2d 1593, 1602 fn29 (Fed. Cir. 1987).

Considering the references cited by the examiner, Applicants point out that claims 1 and 2 of Kojiri, et al., are directed to the indolocarbazole derivative *per se*, not to any combination of that derivative with other antitumor agents. There is no teaching or suggestion in Kojiri, et al., to any combination of the indolocarbazole derivative with any other active agent. As such, no prima facie case for obviousness has been established. *In re Dow Chemical, Co.*

Accepting, for the sake of argument, the examiner's position that NB-506 of Fukuda, et al. is structurally similar to the

compound of Formula IA as claimed herein, Fukuda is specifically limited to a combination of NB-506 with cisplatin (CDDP). There is no teaching in the reference of a combination of the NB-506 or the indolocarbazole of Applicants' formula IA with an antitumor agent selected from the group consisting of 5-fluorouracil, doxorubicin, etoposide, irinotecan, topotecan and campthotecin, with the possible inclusion, in accordance with the proviso of 5-fluorouracil being present, of leucovorin, as is now recited in claims 1, 14 and 34.

Indeed, the study presented by Fukuda, et al., is directed to the effect of cisplatin (CDDP) in combination only with CPT-11, SN-38, an active metabolite of CPT-11 and NB-506 in two drug combinations, i.e., CDDP and NB-506, CDDP and CPT-11, and CDDP and SN-38, while noting that combinations do not always enhance antitumor effect: for example, "However, CPT-11 did not always enhance the antitumor effect of CDDP significantly in mice *in vivo* (25, 26)." (Page 791, lines 22-24). In addition, "... some CPT and CPT-11 resistant cell lines show cross resistance to NB-506 (27)." (Page 791, lines 36-37). Thus, Applicants respectfully submit that there is nothing in Fukuda, et al., to teach a combination of NB-506 or, by association, the compound of Kojiri, et al., with any additional anticancer agent other than cisplatin (CDDP). Furthermore, the fact that Kojiri, et al., teach an indolopyrrolocarbazole derivative including the compound IA as being a useful antitumor agent does not imply an

expectation of suitability in combination with other antitumor agents. Indeed, the statement in Fukuda with respect to the failure of CPT-11 to enhance anti-tumor effect supports this position.

Applicants therefore respectfully submit that the combination of Kojiri, et al, and Fukuda, et al., as cited by the examiner, is limited to the combination of NB-506 or, by association, the compound of Kojiri, et al., and cisplatin (CDDP) and neither teaches nor suggests the combination of Applicants' formula IA with an antitumor agent selected from the group consisting of 5-fluorouracil, doxorubicin, etoposide, irinotecan, topotecan and campthotecin, as recited in the claims amended herein. Thus, the Examiner has improperly used Applicants' disclosure as a blueprint to reconstruct the prior art. *Heidelberger Druckmaschinenag.*

Furthermore, the present claims, as amended herein, recite, in the case of claim 1, "a combined preparation … comprising two separate preparations …" where one preparation is the indolocarbazole and the second preparation comprises at least one antitumor agent selected from the listed group. Claim 14 recites "a method for cancer treatment comprising … administering to a cancer patient: (a) a therapeutically effective amount of …" the indolocarbazole and "(b) a therapeutically effective amount of at least one antitumor agent selected from the group …". Claim 34 recites "a pharmaceutical composition comprising … (a) a

therapeutically effective amount of …" the indolocarbazole and "(b) a therapeutically effective amount of at least one antitumor agent selected from the group …". In each instance, the indolocarbazole is combined with an additional antitumor agent which is at least one of the group consisting of 5-fluorouracil, doxorubicin, etoposide, irinotecan, topotecan, and campthotecin, or a pharmaceutically acceptable salt thereof. That additional antitumor agent is required to be present as indicated by the use of the combining term "and" in the claims. Without that at least one additional antitumor agent, the present invention does not exist.

Applicants respectfully submit that since the present claims, as amended, positively require an additional element that is neither disclosed nor suggested by the Kojiri, et al., reference or the Fukuda, et al., reference, nor is required by claims 1 and 2 of the Kojiri, et al., reference, the present claims, as herein amended, are more limiting than the claims of Kojiri, et al., and are neither taught nor suggested by the combination of Kojiri, et al.,and Fukuda, et al., and cannot be seen as extending the right to exclude one from making and/or using the invention that is defined by the claims of Kojiri, et al., i.e., the indolocarbazole derivative by itself.

In view of the foregoing, Applicants respectfully submit that the claims of the present invention as amended herein are in the nature of an improvement over the invention of Kojiri, et

al., and neither exclude one from making or using the invention of Kojiri, et al, nor extend that right to exclude. Accordingly, Applicants respectfully submit that the basis for the rejection on the ground of nonstatutory obviousness-type double patenting is without support and should be withdrawn.

Claim Rejections 35 USC §103

The rejection of Claims 1, 11-12, 14 and 34 under 35 U.S.C. 103(a) as being unpatentable over Fukuda, et al. (art of record) in view of Kojiri, et al., U.S. 5,922,860 has been maintained for reasons of record. The office action states:

> "The claims of the instant application are drawn to combinations of an indolocarbazole of formula I and an additional anticancer agent, such as cisplatin.
>
> Fukuda et al. disclose synergistic combinations of NB-506 and cisplatin (see abstract-discussion on page 791). Fukuda et al. state that the combination of cisplatin and a topoisomerase I inhibitor has a very interesting strategy for cancer chemotherapy (discussion). What is not taught is the specific compound of formula Ia.
>
> Kojiri et al. teach that compounds having the same formula as those of formula Ia of the instant application and their use as antitumor agents (see claim 2, abstract, examples).
>
> It would have been obvious to one of ordinary skill in the art at the time of the invention to use the topoisomerase I inhibitors of Kojiri et al. in combination with cisplatin with these references before them. Fukuda et al. discuss the potential for synergism in cancer therapy when using cisplatin and a topoisomerase I inhibitor. Morover, it is noted that the compounds of formula Ia are very structurally similar to NB-506, as discussed above. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same

purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. ***In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)***. (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious). See also ***In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960)***(Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and ***Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992)***(mixture of two known herbicides held prima facie obvious). Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the art disclosed indolocarbazole of Kojiri et al. with another antitumor agent, especially in light of the synergistic effects shown by Fukuda et al. One would have been motivated to combine these agents to form a new composition which would be used for the very same purpose, as an antitumor agent. Moreover, it is noted that the KSR decision forecloses the decision that teaching/suggestion/motivation is required in making an obviousness rejection.

Applicants argue that Kojiri et al. do not teach any combinations. Applicants also argue that Fukuda teaches combinations of NB-506 and additional cancer agents, but NB-506 is divergent in structure as compared to the instant compound of formula Ia. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed.Cir. 1986). The examiner believes that due to the close structural relationship between NB-506 as set forth in Fukuda and formula Ia as in Kojiri, a skilled artisan would find it obvious to make a combination of anticancer drugs with the compound of Kojiri and additional agents of Fukuda with these references before them. Regarding applicant's arguments drawn to Fukuda only guessing about the synergistic effects, this would at the minimum afford a skilled artisan an

obvious reason to try to combine the agents as instantly claimed.

Applicants also argue that the structures of formula Ia and NB-506 are very different. The examiner respectfully disagrees. Regarding applicants noting that the instant compounds have -OH in the 2 and 10 positions and NB-506 has -OH in the 1 and 11 positions, it is noted that claim 1 of Kojiri states that the -OH groups can be either in the 1 and 11 positions or the 2 and 10 positions, thus providing obviousness and motivation to have -OH at either sets of locations. The other difference is groups attached to the exocyclic amino moiety, NH-CHO versus $NH\text{-}CH(CH_2OH)_2$. However, Kojiri et al. also bridges the gap as the results of Table 1 show compounds with NH-CHO group have slightly lower activity versus compounds with $NH\text{-}CH(CH_2OH)_2$ groups attached. Thus rendering obvious and providing motivation to change the NH-CHO to a $NH\text{-}CH(CH_2OH)_2$ group.

Regarding applicant's arguments drawn to a "synergistic combination", it is noted these limitations are not in the claims and as such are not deemed to render unobvious the instant rejection. And these synergistic effects are not deemed unobvious as Fukuda et al. discusses synergism between their NB-506 compound and additional anticancer agents such as cisplatin."

In view of the herein presented amendments to claims 1, 11-12, 14 and 34, Applicants respectfully traverse the rejection because the prima *facie case* of obviousness has not been established.

Applicants respectfully submit that there is no teaching or suggestion in the references as applied which would lead one of ordinary skill in the art to combine the compound of Formula IA or NB-506 with an additional antitumor agent which is at least one of the group consisting of 5-fluorouracil, doxorubicin, etoposide, irinotecan, topotecan, and campthotecin, or a pharmaceutically acceptable salt thereof as now recited.

Applicants respectfully submit that, as pointed out in connection with the rejection on the ground of nonstatutory obviousness-type double patenting, Fukuda, et al., is limited to a disclosure of a combination of NB-506 with cisplatin (CDDP), Fukuda, et al., being directed to a study of the effect of cisplatin (CDDP) alone or in combination with a specifically recited set of additional agents, *to wit*, NB-506, CPT-11 and SN-38, in two drug combinations. As such, the study presented by Fukuda, et al., demonstrates the use of cisplatin (CDDP) combined only with CPT-11, SN-38, an active metabolite of CPT-11 or NB-506, not the combination of NB-506 or any analogue thereof with other unlisted agents. There is no way to construe these prior art references as reading on the cited claims without relying upon Applicants' own disclosure to provide the "instruction book" to do so. *Panduit Corp.* Even if that were appropriate, as explained above, the ground of rejection still lacks a teaching of the combination of NB-506 or any analogue thereof with other unlisted agents.

As amended herein, the claimed invention is directed to combinations of the indolopyrrolocarbazole compound of Formula IA, an inhibitor of DNA topoisomerase inhibitor I, and an additional anticancer agent selected from the following:

(i) 5-fluorouracil (5-FU, which is classified as an "antitumor metabolite" and is preferably used in combination with leucovorin;

(ii) Etoposide which is classified as a "plant-derived antitumor agent";

(iii) Doxorubicin (adriamycin) which is classified as an "antitumor antibiotic"; and

(iv) Irinotecan, topotecan and campthotecin which are classified as "antitumor campthotecin derivatives".

Kojiri, et al., merely teach an indolopyrrolocarbazole derivative, including the compound of Formula IA, without reference to its use in combination with any other anticancer agent or to any synergistic effect which such a combination may exhibit. As the examiner states, what is not taught in Kojiri, et al., is the combination of the indolopyrrolocarbazole derivative with additional anticancer agents. For this, the examiner relies on the teaching of Fukuda, et al.

Accepting, for this argument, that the compound of Formula IA and the indolocarbazole NB-506 of Fukuda, et al., are analogous, Applicants respectfully point out that Fukuda, et al., only teach the ND-506 in combination with cisplatin (CDDP). There is no mention of the additional anticancer agents recited in claims 1, 14 and 34, as amended herein, i.e., the group consisting of 5-fluorouracil, doxorubicin, etoposide, irinotecan, topotecan, and campthotecin. Note that, with respect to campthotecin, Fukuda, et al., do not teach the combination of CPT-11 with NB-506. Rather, the combinations of the additional

agents, NB-506, CPT-11 and SN-38 of Fukuda, et al., are with cisplatin (CDDP) and not with each other.

Indeed, the study presented by Fukuda, et al., while directed to the effect of cisplatin (CDDP) in combination only with CPT-11, SN-38, an active metabolite of CPT-11 and NB-506 in two drug combinations, i.e., CDDP and NB-506, CDDP and CPT-11, and CDDP and SN-38, notes that combinations do not always enhance antitumor effect: for example, "However, CPT-11 did not always enhance the antitumor effect of CDDP significantly in mice *in vivo* (25, 26)." (Page 791, lines 22-24). In addition, "... some CPT and CPT-11 resistant cell lines show cross resistance to NB-506 (27)." (Page 791, lines 36-37). Thus, Applicants respectfully submit that there is nothing in Fukuda, et al., to teach a combination of NB-506 or, by association, the compound of Kojiri, et al., with any additional anticancer agent other than cisplatin (CDDP). Indeed, as noted above, there is support to suggest that a combination of NB-506 or, by association, the compound of Formula IA with other anticancer agents, e.g., CPT or CPT-11, would neither be obvious nor synergistic. Furthermore, the fact that Kojiri, et al., teach an indolopyrrolocarbazole derivative including the compound IA as being a useful antitumor agent does not imply an expectation of suitability in combination with other antitumor agents. Indeed, the statement in Fukuda with respect to the failure of CPT-11 to enhance antitumor effect supports this position.

With regard to the arguments based on synergistic effect, Applicants merely wished to point out that the present invention showed evidence of unexpected synergistic effect in the combination of the compound of Formula IA with the additional anticancer agents listed in the claims such that the recited combinations would not be obvious to one of ordinary skill in the art. Indeed, whereas Fukuda, et al., indicates that there can be cross resistance with CPT-11 and NB-506, Table 1 of the specification of the present invention shows that the compound of Formula IA exhibits a synergistic effect in combination with campthotecin or doxorubicin (adriamycin). Similarly, Table 2 shows that the combination of the compound of Formula IA and doxorubicin (adriamycin) or etoposide exhibit a synergistic antitumor effect. Furthermore, the claimed combination of the compound of Formula IA and 5-FU/leucovorin shows a significant inhibition of tumor growth as evidenced by the results shown in Fig. 3. Additionally, Tables 5 and 6 and Example 4 of the present specification show that the combination of the compound of Formula IA with doxorubicin (adriamycin) can significantly decrease the amount of each drug needed and exhibits reduced side effects. Neither effect is suggested or taught by Kojiri, et al., or Fukuda, et al., either singly or in combination, nor is there any disclosure in either reference which would lead one of ordinary skill in the art to expect such results from the combinations recited in the presently amended claims.

Accordingly, Applicants respectfully submit that the claims as amended herein are not obvious over the cited references and that the rejection under 35 U.S.C. §103(a) has been overcome and should be withdrawn.

In view of the foregoing, Applicants respectfully submit that the present grounds of rejection are either without support or have been overcome and should be withdrawn and that claims 1, 11, 12, 14 and 34 as amended herein are allowable over the prior art.

Although this Amendment is presented after a Final Rejection, it is respectfully submitted that it should be entered. The Amendment reduces the issues that would be present on Appeal by deleting limitations from independent Claim 1 and claims dependent therefrom to further limit the invention and distinguish from the prior art. Deletion of these terms does not require further consideration or search since the terms were searched when they were included in the claims. For the reasons set forth above, the claims as amended patentably distinguish from the prior art applied thereagainst as well as with regard to the obviousness type double patenting rejection.

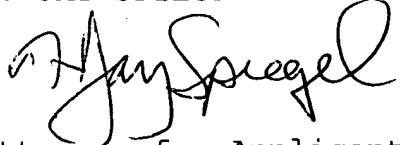
As such, for these reasons, even if the Examiner believes the claims as amended are not patentable, the claims as amended do reduce the issues that would be present upon Appeal. As such, for these reasons, the Amendment should be entered and for the

reasons set forth above, as a result of the amendments, the claims should be allowed.

An early notice of allowance is respectfully requested.

Respectfully submitted,

H. JAY SPIEGEL & ASSOCIATES



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